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Does the course of laboratory parameters help us to predict the outcome of CCHF?

Sümeyye KAZANCIOĞLU[1,*], Esragül AKINCI[2], Aliye BAŞTUĞ[2], Bircan KAYAASLAN[3], Ayşe BUT[2], Halide ASLANER[2], Selim Sırrı EREN[2], Meltem Arzu YETKİN[2], Hurrem BODUR[2]

[1]Department of Infectious Diseases and Clinical Microbiology, Niksar State Hospital, Tokat, Turkey
[2]Department of Infectious Diseases and Clinical Microbiology, Ankara Numune Research and Training Hospital, Ankara, Turkey
[3]Department of Infectious Diseases and Clinical Microbiology, Faculty of Medicine, Yıldırım Beyazıt University, Ankara, Turkey

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Abstrat

Background/aim: This study was performed to identify the characteristics distinguishing fatal and nonfatal cases of patients diagnosed with Crimean–Congo hemorrhagic fever (CCHF).

Materials and methods: A total of 92 patients with confirmed diagnosis of CCHF in 2009–2013 were included in the study.

Results: A high level of urea and aPTT on the third day of hospital stay, diarrhea, somnolence, and the interval from the beginning of the symptoms to hospital admission were independently associated with fatality. Each 10-unit increase in aPTT and urea levels increased the fatality rate by 3.379-fold and 1.236-fold, respectively. Delay in hospital admission increased the fatality rate 1.453-fold for each day of delay. When comparing first and third admission-day laboratory values, the increase in leukocyte counts and the decrease in CPK, urea, creatinine, aPTT, PT, INR, and hemoglobin levels were significant in nonfatal cases.

Conclusion: This study showed that the course of these laboratory tests helps us to predict the outcome of the disease. In a few days of hospitalization, persistence or progress of the abnormal laboratory parameters may warn us about poor prognosis.

Key words: Crimean–Congo hemorrhagic fever, mortality, severity criteria

1. Introduction

Crimean–Congo hemorrhagic fever (CCHF) is a tick-borne disease caused by a *Nairovirus* of the *Bunyaviridae* family (1). The disease is endemic or potentially endemic in 52 countries (2). Since 2002, CCHF has been a serious problem in the central, northern, and eastern regions of Turkey. Although the number of cases has increased year by year, the case fatality rate has been reported as 5% on average (3).

The clinical spectrum of CCHF varies from asymptomatic or mild infections to severe disease and death (4). In severe cases, hemorrhagic manifestations develop 3–6 days after the onset of the illness. The mortality rate is very broad, depending on the geographic region. It has been reported to be between 5% and 30% in different studies (3,5). The outcome of the disease is correlated with high viral load (>10^8 copies/mL), abnormal laboratory values (thrombocytopenia, leucocytosis, elevated liver enzymes, high CPK levels, prolonged aPTT, high INR, etc.), and severe clinical signs or symptoms (hematemesis, melena, hematuria, petechiae, somnolence, etc.) (6).

This study was performed to identify the different characteristics of fatal and nonfatal cases and the factors increasing the fatality rate of CCHF. The laboratory parameters were also evaluated day by day after hospital admission, and the effect of the changes in these parameters for predicting the outcome was investigated.

2. Materials and methods

This retrospective study was carried out at the Ankara Numune Education and Training Hospital, which is a referral and tertiary care hospital in Turkey. A total of 92 patients with confirmed diagnosis of CCHF during 2009–2013 were included in the study. These patients had compatible clinical presentation with CCHF and positive viral RNA by RT-PCR or specific IgM antibodies by ELISA in serum samples. Data of the patients was collected from specifically designed follow-up charts and patient files. Demographic, epidemiological, and clinical characteristics, laboratory parameters, and treatment and outcome of the patients were analyzed statistically. A comparison was made between the characteristics of

* Correspondence: sumeyye_yildiz@hotmail.com

deceased and surviving patients, and the risk factors for mortality were determined. In addition, the first and the third admission-day laboratory parameters were evaluated and the effect of the difference on the outcome was established.

2.1. Statistical analysis

Patients were classified into 2 groups according to their survival status: deceased, or discharged with recovery. SPSS 11.5 was used for statistical analysis. The Kolmogorov–Smirnov test was used for numeric variables if they were close to normal. The numeric data was expressed as median (min–max) and medium, and the categorical data as number and percentages. Student's test and the Mann–Whitney U test were used for median and medium variables with groups. Pearson's chi-square test or Fisher's exact test was used for categorical variables. First and third day laboratory values were compared using the dependent t-test and Wilcoxon test. Receiver operating characteristic (ROC) curve analysis was performed for values that were statistically significant. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated. Cox regression was used to model outcomes. The time start-point was the patient's admission to the hospital and the time end-point was either death or discharge from hospital. For multivariate analysis, $P < 0.25$ in univariate analyses was tested to determine independent risk factors.

3. Results

The mean age of the patients was 50 years, and 46 (50%) were male. Eighty-one patients (88.0%) were involved in handling livestock or farming. A history of tick bites was present for 64 patients (69.6%). Of the 92 patients, 15 died and 77 survived. The case fatality rate was 16.3%. Fatal cases were hospitalized for a mean of 4 days (range: 1–8) before death.

Age, sex, tick contact, time from tick bite to appearance of complaints, and comorbidities were similar between fatal and nonfatal groups ($P > 0.05$). Duration of hospital stay was shorter and the interval from the beginning of symptoms to hospital admission was longer in fatal cases ($P = 0.01$ and $P = 0.007$, respectively). Diarrhea, shortness of breath, skin eruptions, bleeding, fever, and somnolence were significantly more common in patients who died (Table 1). Biochemical and hematological laboratory values of the 2 groups were also compared to determine fatality predictors. In fatal cases, platelet count and fibrinogen were significantly lower, whereas ALT, AST, LDH, urea, aPTT, PT, and INR were significantly higher than in nonfatal cases on both the first and the third admission days (Table 2).

Among 48 patients who underwent abdominal ultrasonography (US), 18 (38%) had abnormal findings. The most common US findings were pericholecystic fluid and an increase in the thickness of the gallbladder wall (13/18 patients). Nine patients had hepatomegaly. Splenomegaly was detected in 4 patients. Among 86 patients with PA chest X-rays, 17 (20%) had radiological abnormalities. These X-ray and US findings were observed to be higher in the fatal group than in the nonfatal group (Table 3). In 9 patients with somnolence, cranial computed tomography (CT) was performed, although no pathological findings were detected.

All patients in this study received only supportive therapy. Nearly half of the patients (n = 45, 49%) received blood or blood product infusions. Antibiotic treatment was started for one-third of the patients with the suspicion of secondary bacterial infections. Almost all fatal cases (14/15) had one or more complications. The rates of antibiotic therapy, blood transfusion, and complications were significantly higher in fatal cases (Table 3).

In comparing the first and third admission-day laboratory values, an increase of WBC counts and the decrease of CPK, urea, creatinine, aPTT, PT, INR, and Hb levels were significant in nonfatal cases. However, there was no significant difference between the first and third admission-day laboratory values in the fatal group (Table 4).

ROC curve analysis was performed for all the statistically significant parameters. Obtained cut-off values are presented in Table 5. The Cox model was used for fatality analysis. The time start-point was admission to the hospital and the end-point was either death or discharge from hospital. Urea and aPTT on the third admission day, diarrhea, somnolence, and the interval from the beginning of the symptoms to hospital admission were independently associated with fatality. Each 10-unit increase in aPTT and urea levels increased the fatality rate 3.379-fold and 1.236-fold, respectively. In addition, delay of admission to hospital increased the fatality rate 1.453-fold for each day (Table 6).

4. Discussion

CCHF is an endemic disease in rural areas of Turkey. One major risk group is farmers, and the most common method of transmission is exposure to ticks (3,7). A history of tick bite was reported as 68.7% in Turkish patients, similarly to this study (3). Initial symptoms of CCHF are nonspecific, characterized by fever, weakness, headache, myalgia, nausea, and vomiting. In severe cases, hemorrhages develop 3–6 days after the onset of the disease (4,8). In this study, one of the prominent symptoms was skin lesion, which was more common in comparison with our previous study (8). Skin lesions were detected in 41% of our patients and petechiae were the most frequent type. Akyol et al. evaluated 35 patients and found that 83.3% of the

Table 1. Demographic, epidemiological, and clinical characteristics of CCHF patients.

Characteristics	Total cases (%) n = 92	Nonfatal cases (%) n = 77	Fatal cases (%) n = 15	P-value
Male	46 (50)	37/77 (48.1)	9/15 (60.0)	0.397
Age, years (mean)	49.4 ± 17.4	48.3 ± 18.0	55.1 ± 13.2	0.166
Living in rural areas	85 (92.4)	71 (92.2)	14 (93.3)	1.000
Handling livestock/farming	81 (88.0)	67 (87.0)	14 (93.3)	0.685
Tick exposure	64 (69.6)	55 (71.4)	9 (60.0)	0.376
Time from tick bite to onset of complaints (days)	3.8 ± 2.8	3.9 ± 2.8	3.3 ± 3.04	0.489
Interval from the beginning of symptoms to hospital admission (days)	2.7 ± 2.1	2.5 ± 2.1	3.9 ± 2.2	0.007
Comorbidities	21 (22.8)	15 (19.5)	6 (40.0)	0.099
Hospital stay (days)	6.7 ± 3.7	7 ± 3. 4	4 ± 2.8	0.010
Symptoms				
Fever	80 (87)	66 (85.7)	14 (93.3)	0.683
Fatigue	85 (92.4)	71 (92.2)	14 (93.3)	1.000
Nausea/vomiting	58 (63)	46 (59.7)	12 (80.0)	0.137
Diarrhea	26 (28.3)	15 (19.5)	11 (73.3)	<0.001
Headache	53 (57.6)	41 (53.2)	12 (80.0)	0.055
Shortness of breath	23 (25.0)	16 (20.8)	7 (46.7)	0.050
Skin eruption	38 (41.0)	28 (36.4)	10 (66.7)	0.029
Bleeding (any kind)	28 (30.4)	18 (23.4)	10 (66.7)	0.002
Clinical findings				
Fever, temperature >38 °C	44 (47.8)	33 (42.9)	11 (73.3)	0.031
Somnolence	9 (9.8)	3 (3.9)	6 (40.0)	<0.001
Respiratory abnormalities	21 (23.0)	13 (16.9)	8 (53.3)	0.005
Hepatosplenomegaly	7 (8.0)	6 (7.8)	1 (6.7)	1.000
Skin lesions				
Petechiae	32 (35.0)	23 (29.9)	9 (60.0)	0.025
Ecchymosis	16 (17.0)	10 (13.0)	6 (40.0)	0.021
Maculopapular rash	7 (8.0)	6 (7.8)	1 (6.7)	1.000
Bleeding				
Epistaxis	10 (10.9)	8 (10.4)	2 (13.3)	0.664
Gingival bleeding	12 (13.0)	8 (10.4)	4 (26.7)	0.103
Melena	10 (10.9)	3 (3.9)	7 (46.7)	<0.001
Vaginal bleeding	4 (4.3)	3 (3.9)	1 (6.7)	0.516
Hematemesis	3 (3.3)	1 (1.3)	2 (13.3)	0.068
Subcutaneous hematoma	4 (4.3)	2 (2.6)	2 (13.3)	0.123
Hematuria	10 (10.9)	5 (6.5)	5 (33.3)	0.009

Table 2. Comparison of laboratory findings in fatal and nonfatal cases.

	First day			Third day		
	Nonfatal cases (n = 77)	Fatal cases (n = 15)	P-value	Nonfatal cases (n = 77)	Fatal cases (n = 15)	P-value
WBC (/μL)	2899 ± 2183	4935 ± 4152	0.052	3196 ± 1737	4100 ± 3459	0.917
Hb (g/dL)	13.4 ± 1.92	13.3 ± 2.97	0.940	12.9 ± 1.79	11.7 ± 2.42	0.034
PLT (/μL)	79,610 ± 59,725	27,571 ± 13,754	<0.001	73,610 ± 46,811	31,714 ± 31,145	<0.001
ALT (U/L)	92 ± 84	210 ± 218	0.016	110 ± 114	331 ± 339	<0.001
AST (U/L)	195 ± 187	699 ± 764	<0.001	245 ± 436	1081 ± 1006	<0.001
CPK (U/L)	564 ± 836	1111 ± 1246	0.129	379 ± 692	2205 ± 3349	<0.001
LDH (U/L)	541 ± 381	1561 ± 1227	<0.001	657 ± 1018	1572 ± 703	<0.001
Creatinine (mg/dL)	0.99 ± 0.91	1.4 ± 1.05	0.025	0.90 ± 0.89	1.7 ± 1.43	<0.001
Urea (mg/dL)	31.7 ± 24.8	62.3 ± 50.78	0.002	24.7 ± 14.8	71.5 ± 57.94	<0.001
aPTT (s)	36.3 ± 9.09	55.0 ± 13.38	<0.001	32.6 ± 6.9	53.7 ± 14.16	<0.001
PT (s)	12.8 ± 1.69	15.2 ± 2.64	<0.001	11.9 ± 1.59	14.9 ± 4.38	<0.001
INR	1.0 ± 0.15	1.3 ± 0.22	<0.001	1.0 ± 0.10	1.3 ± 0.38	<0.001
Fibrinogen (mg/dL)	281 ± 84	207 ± 71	<0.001	290 ± 85	218 ± 94	0.013

P < 0.025 was considered statistically significant.
WBC: White blood cells; Hb: hemoglobin; PLT: platelet; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CPK: creatine phosphokinase; LDH: lactate dehydrogenase; aPTT: activated partial thromboplastin time; PT: prothrombin time; INR: international normalized ratio.
CRP and D-Dimer were tested only on the first day. They were not found to be associated with fatality. P-values were 0.963 and 0.294, respectively.

Table 3. Radiological characteristics, complications, and treatment of CCHF patients

Characteristics	All cases (%)	Nonfatal cases (%)	Fatal cases (%)	P-value
US abnormality	18/48 (38.0)	12/41 (29.3)	6/7 (85.7)	0.008
Chest X-ray abnormality	17/86 (20.0)	10/73 (13.7)	7/13 (53.8)	0.003
Antibiotic treatment	28/92 (30.0)	16 (20.8)	12 (80.0)	<0.001
Transfusion	45/92 (49.0)	30 (39.0)	12 (80.0)	<0.001
Complications (any kind)	34/92 (36.9)	20 (26.0)	14 (93.3)	<0.001
Bleeding	20/92 (21.7)	9 (11.7)	11 (73.3)	<0.001
Secondary infections	20/92 (21.7)	11 (14.3)	9 (60.0)	<0.001
Renal failure	14/92 (15.2)	4 (5.2)	10 (66.7)	<0.001
Mechanical ventilation	8/92 (8.7)	0 (0.0)	8 (53.3)	<0.001

Table 4. Comparison of the first and third admission-day laboratory values in nonfatal and fatal groups.

	Nonfatal cases (n = 77)			Fatal cases (n = 15)		
	First day	Third day	P-value	First day	Third day	P-value*
WBC (/μL)	2899 ± 2183	3196 ± 1737	0.022	4935 ± 4152	4100 ± 3459	0.084
Hb (mg/dL)	13.4 ± 1.92	12.9 ± 1.79	0.002	13.3 ± 2.97	11.7 ± 2.42	0.050
PLT (/μL)	79,610 ± 59,725	73,610 ± 46,811	0.724	27,571 ± 13,754	31,714 ± 31,145	0.572
ALT (U/L)	92 ± 84	110 ± 114	0.370	210 ± 218	331 ± 339	0.064
AST (U/L)	195 ± 187	245 ± 436	0.566	699 ± 764	1081 ± 1006	0.198
CPK (U/L)	564 ± 836	379 ± 692	<0.001	1111 ± 1246	2205 ± 3349	0.028
LDH (U/L)	541 ± 381	657 ± 1018	0.843	1561 ± 1227	1572 ± 703	0.551
Creatinine (mg/dL)	0.99 ± 0.91	0.90 ± 0.89	<0.001	1.4 ± 1.05	1.7 ± 1.43	0.258
Urea (mg/dL)	31.7 ± 24.8	24.7 ± 14.8	<0.001	62.3 ± 50.78	71.5 ± 57.94	0.233
aPTT (s)	36.3 ± 9.09	32.6 ± 6.9	<0.001	55.0 ± 13.38	53.7 ± 14.16	0.730
PT (s)	12.8 ± 1.69	11.9 ± 1.59	<0.001	15.2 ± 2.64	14.9 ± 4.38	0.727
INR	1.0 ± 0.15	1.0 ± 0.10	<0.001	1.3 ± 0.22	1.3 ± 0.38	0.875
Fibrinogen (mg/dL)	281 ± 84	290 ± 85	0.094	207 ± 71	218 ± 94	0.451

*P < 0.025 was considered statistically significant.

Table 5. Cut-off levels for prognostic factors.

	First day				Third day			
	Level	Sensitivity Specificity	PPV NPV	AUROC	Level	Sensitivity Specificity	PPV NPV	AUROC
PLT (/μL)	<30,000	85.7 81.8	46.2 96.9	0.840	<29,500	78.6 80.5	42.3 95.4	0.801
ALT (U/L)	>103	71.4 72.7	32.3 93.3	0.704	>105	85.7 64.9	30.8 96.2	0.815
AST (U/L)	>222	78.6 70.1	32.4 94.7	0.790	>331	85.7 83.1	48.0 97.0	0.896
CPK (U/L)	-	-	-	-	>566	78.6 83.1	45.8 95.5	0.859
LDH (U/L)	>961	64.3 85.7	45.0 93.0	0.800	>709	100 75.3	42.4 100	0.899
Creatinine (mg/dL)	-	-	-	-	1.13	57.1 93.5	61.5 92.3	0.769
Urea (mg/dL)	>27.5	92.9 58.4	28.9 97.8	0.760	>26.5	100 64.9	34.1 100	0.901
aPTT (s)	>53.1	71.4 94.8	71.4 94.8	0.884	>37.6	92.9 84.4	52.0 98.5	0.932
PT (s)	>13.2	78.6 71.4	33.3 94.8	0.793	>12.95	71.4 88.3	52.6 94.4	0.843
INR	>1.06	85.7 55.8	26.1 95.6	0.768	>1.05	78.6 79.2	40.7 95.3	0.817
Fibrinogen (mg/dL)	<226	71.4 80.5	40.0 93.9	0.773	<227	64.3 81.8	39.1 92.6	0.710

Table 6. The evaluation of all possible risk factors on survival (multivariate logistic regression analysis).

	Odds ratio	95% CI	P-value
aPTT (s) (third day)*	3.379	1.758–6.494	<0.001
Urea (mg/dL) (third day)*	1.236	1.066–1.433	0.005
Diarrhea	6.875	1.600–29.538	0.010
Somnolence	6.310	1.531–25.999	0.011
Interval from the beginning of symptoms to hospital admission, days**	1.453	1.058–1.995	0.021

*Effect on fatality for each 10-unit increase.
**Effect on fatality for each day of admission delay.

patients had one or multiple skin lesions (9). They reported ecchymosis as 65.7%, petechiae or purpura as 57.1%, and morbilliform rash as 31.4%. They also emphasized that these lesions were seen at higher rates in extremities open to trauma. The other striking symptom of our patients was respiratory system findings. The rate for shortness of breath was 25%, auscultation abnormalities were 23%, and chest radiographic abnormalities were 19.8% in 86 patients. Radiographic pulmonary abnormalities were more common in fatal cases. There are a few studies about respiratory system involvement in CCHF patients. In one of these studies, it was emphasized that cough and dyspnea were more common symptoms and ARDS could occur in patients with hemoptysis (10). Dogan et al. reported pathological auscultation findings as 33.4% (crackles: 31.5%, rhonchi: 1.9%) and chest radiographic abnormalities as 33.3% (infiltrations: 17.6%) in CCHF patients (11). They also found that respiratory complaints were more common in patients who died. In this study, gastrointestinal ultrasonic findings were also noteworthy. Nearly one-third of the patients had an increase in the thickness of the gallbladder wall and pericholecystic fluid in their abdominal US imaging. Additionally, these findings were more frequent in the fatal group. There is no publication about radiological imaging of the abdomen in CCHF. Thus, the precise involvement of the gastrointestinal system with CCHF is not known.

CCHF is a fatal hemorrhagic syndrome. Reported fatality rates range between 5% and 30% in different studies (5,6). In this study, the fatality rate was found to be 16.3%, which is higher than the average rate (5%) in Turkey (12). Our hospital is one of the referral hospitals for CCHF patients and mostly had severe cases transferred to receive more intensive supportive treatment. Thus, our fatality rate is above the average rate of Turkey. In this study, diarrhea, shortness of breath, petechiae, ecchymosis, and bleeding were found to be significantly more common in the fatal group. Bleeding is an important factor for prognosis. Nearly 30% of patients had complaints of hemorrhage upon admission to hospital. Skin bleeding was more common, including petechiae (34.8%), ecchymosis (17.4%), and subcutaneous hematoma (4.3%). Melena, hematuria, petechiae, and ecchymosis were significantly more frequent in fatal cases. In several studies, the outcome of the disease was shown to be correlated significantly with somnolence and gastrointestinal bleeding (8,13,14).

There were statistically significant differences between the 2 groups in clinical and laboratory variables. ALT, AST, LDH, urea, aPTT, PT, and INR were significantly higher in the fatal group, whereas platelet count and fibrinogen were significantly lower. Although WBC count was higher in the fatal group, there was no significant difference compared to the nonfatal group. However, Swanepoel et al. and Hatipoglu et al. found that high WBC count was a predictor of fatality (13,14).

Cut-off levels of prognostic factors can help us to predict the outcome of the disease. Platelet count and aPTT are the mostly used predictive factors. In this study, platelet counts lower than $<30 \times 10^9$/L and aPTT higher than 53.1 s were predictors of survival with high specificity (81.8% and 94.8%) and high negative predictive value (96.9% and 94.8%). There are different cut-off levels in the literature. Ozturk et al. reported that aPTT of >65.7 s and platelet counts of $>17 \times 10^9$/L were predictors of survival (15). Yılmaz et al. and Çevik et al. reported cut-off levels of platelet counts of $<90 \times 10^9$/L and $<20 \times 10^9$/L and aPTT levels of >34 s and >60 s for risk factors of mortality, respectively (16). In our study, it was shown that the third admission-day's aPTT cut-off level (37.6 s) was more important for prognosis of the disease (specificity 92.9%, sensitivity 84.4%, NPV 98.5%).

When all possible risk factors for survival were evaluated by multivariate logistic regression analysis, the 5 most important survival parameters were, in order, the third day's aPTT and urea levels, somnolence, complaints of diarrhea, and duration of complaints prior

to hospitalization. A 10-unit increase of aPTT and urea was associated with a 3.379-fold and 1.236-fold increase in fatality rate, respectively. Each day of admission delay was found to elevate fatality rate 1.453-fold. This means that earlier admission to the hospital significantly improves the patients' outcome. Thus, it is important to provide awareness and education to people living in endemic areas. In other similar studies, somnolence, diarrhea, melena, hematemesis, hematuria, elevated ALT and LDH, prolonged aPTT, and decreased platelet count were found as independent predictors associated with fatality by multivariate analysis (8,14). High viral load was reported as one of the most significant factors affecting the mortality rate in CCHF (17). However, viral loads of the patients could not be evaluated in this study, which is a weakness of our study. The reason is that this is a retrospective study; therefore, quantitative PCR could not be performed for most of the patients.

In previous studies, deaths were reported to occur between days 5 and 14 of the disease. In our patients, deaths generally occurred on day 4 of hospitalization. Thus, we analyzed the first and the third admission-day laboratory parameters to find out the clinical significance of the laboratory difference between the two days in fatal and nonfatal cases. When the first and the third admission-day laboratory values were compared, increase of WBC counts and decrease of CPK, urea, creatinine, aPTT, PT, and INR levels were significant in the nonfatal group. However, there was no difference in the fatal group. This result suggests that an improvement in abnormal laboratory values in the 3 days after hospital admission may be a valuable predictor for survival. If there is no significant improvement, this may show us that the outcome is probably poor.

In conclusion, there are many laboratory tests to predict the fatality of patients with CCHF. Additionally, this study showed that the course of these laboratory tests also helps us to predict the outcome of the disease. In a few days of hospitalization, persistence or progress of the abnormal laboratory parameters may warn us about poor prognosis.

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